PATENT
Docket No. 0690-0110P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Wolfgang M. FRANZ et al.	Conf:	2640
APPLN. NO.:	09/068,751	GROUP:	1635
FILED:	November 2, 1998	EXAMINER:	M. Schmidt

FOR: GENE-THERAPEUTIC NUCLEIC ACID CONSTRUCT, PRODUCTION OF SAME AND USE OF SAME IN THE TREATMENT OF HEART DISEASE

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner of Patents
Washington, DC 20231

Sir:

I, Dr. Wolfgang Franz, hereby declare the following in connection with the above-identified U.S. Patent application:

1. I am a citizen of Germany, residing at Gautingerstr. 15 D-82234 Wessling.

2. I am a co-inventor of the subject matter of U.S. patent application no. 09/068,751 and I am familiar with the prosecution history thereof.

3. On November 16, 2001, I participated in an interview with the Examiner regarding the application.

4. In the interview the focus of the discussion of prior art was first upon the Franz reference. In the Franz reference, a construct of the 2.1 kb upstream region of the MLC gene was linked to a luciferase gene and transferred into transgenic mice

through the germ line by oocyte injection. Thus, the gene was present in every cell of the body of the transgenic mouse. Expression of the construct was assessed and cardiac specific expression was found.

On the other hand, the present claims recite that portions of an MLC upstream region that are sufficient for cardiac-specific expression of a desired nucleic acid after administration to somatic cells are linked to that nucleic acid in a viral, preferably an adenoviral or adeno-associated virus, vector. The state of the art at the time the invention was made was such that successful cardiac-specific expression obtained by germ line transmission in no way established that the same sort of construct would provide successful cardiac-specific expression of the same gene when administered to somatic cells.

5. One apparent cause of this unpredictability lies in the use of adenovirus type vectors. As explained during the interview, adenoviruses (and many other mammalian viruses such as lentiviruses) include as part of their genome an inverted terminal repeat sequence (ITR or LTR) and various enhancer elements. These terminal repeats and enhancers can interfere with specificity elements of the inserted gene constructs, leading to unexpected changes in the tissue specificity of

expression of exogenous nucleic acids incorporated into constructs in the vector. Some evidence of this interference is shown by the abstracts presented in Exhibit 1, copies of two abstracts of papers that discuss effects of the adenovirus ITR on tissue specificity. The abstract by Shin et al. shows that an adenovirus ITR has a negative effect on overall expression of a transgene driven by the myosin light chain promoter 1. The abstract by Rubinchik shows that the E1A portion of the adenovirus genome appears to decrease selectivity of expression of transgene promoters.

6. At the time the invention claimed in the above-identified application was made, one of ordinary skill in the art could not, based upon results from germ line transformation experiments, predict that tissue specificity of gene expression of a construct used in the germ line transformation would be retained upon tranformation of somatic cells of an animal by a viral vector containing the same or a similar construct.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

_____ _____

Wolfgang M. Franz, M.D. (date)

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12-3-2001

Wolfgang M. Franz, M.D. (date)

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